DIAGNOSTIC UTILITY OF VENOUS AMMONIA, SPLEEN SIZE AND PLATELET COUNT AS NON INVASIVE MARKERS OF PORTO SYSTEMIC COLLATERALS IN CIRRHOTICS

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CERTIFICATE

This is to certify that this dissertation entitled **"DIAGNOSTIC UTILITY OF VENOUS AMMONIA, SPLEEN SIZE AND PLATELET COUNT AS NON INVASIVE MARKERS OF PORTO SYSTEMIC COLLATERALS IN CIRRHOTICS",** submitted by **S.BABU KUMAR** to the faculty of Medical Gastroenterology, The Tamilnadu Dr.MGR Medical University, Guindy, Chennai-600032, in partial fulfillment of the requirement for the award of DM Degree, Branch IV (Medical Gastroenterology) is a bonafide work carried out by him under my direct supervision and guidance.

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CONTENTS

INTRODUCTION

Portal hypertension is defined as portal pressure gradient of more than 6 mm Hg. The hypertensive portal vein is decompressed by diverting up to 90% of the portal flow through portasystemic collaterals back to the heart resulting in enlargement of these vessels. These vessels are commonly located at the gastro esophageal junction where they lie subjacent to the mucosa and present as gastric and esophageal varices. Duodenum , rectum , retroperitoneum are the other important sites where significant collaterals form due to portal hypertension. However, due to their higher resistance and increased portal venous inflow, these collaterals are unable to decrease the hypertension.

Demonstration of the existence and extent of portosystemic collaterals is important in the management of patients with portal hypertension. The reported prevalence of esophageal varices in cirrhotic patients is variable with figures ranging between 24% and 80%, with a mean of about 60% [1]: The prevalence of varices seems to be related to the degree of liver dysfunction, 30% for compensated patients and of 60% for decompensated patients [2 ,3]. Because of this variability, it has been recommended that all patients with cirrhosis should be evaluated by endoscopy to ascertain the presence of portal hypertension.[4,5].

The risk of developing varices in patients who's initial endoscopy is negative for varices is about 5- 8 % per year [6,8]. The rate of increase of variceal size from small to large is not well defined. Those with small varices tend to develop large varices by about 45% in 2 years time[9,10].

Variceal hemorrhage occurs in 25 to 40 percent of patients with cirrhosis which accounts for 10–30% of all cases of upper gastrointestinal bleeding . [11] .The annual incidence of variceal bleed in a non bleeder is about 4% [12, 13] . Survivors of an episode of active bleeding have a 70 percent risk of recurrent hemorrhage within one year of the bleeding episode [14]

The mortality resulting from any bleeding episode may range from < 10% in well compensated cirrhotic patients with Child–Pugh grade A to > 70% in those in the advanced Child–Pugh C cirrhotic stage.[15- 18] .The risk of re-bleeding is high, reaching 80% within 1 year .In view of the relatively high rate of bleeding from esophageal varices and the high associated mortality, an important goal of management of patients with cirrhosis is the primary prevention of variceal hemorrhage.

There are several medical and surgical modalities available for primary prophylaxis of variceal hemorrhage. These therapies are aimed at

achieving either by decreasing portal hypertension (eg, beta blockers, surgical portal decompression, or transjugular intrahepatic shunt.), or by directly treating the varices themselves (eg, variceal ligation). Beta blockers are effective in primary prevension of variceal bleed but this Randomized trials and meta-analyses show that beta-blockers reduce the number of bleeding events when used as primary prevention in esophageal varices.[19]. However this treatment is not free from side effects.[(20, 21).]

The current recommendations are that follow-up endoscopy should be performed at 2 to 3-year intervals in compensated patients with no varices and at 1- to 2-year intervals in compensated patients with small varices.[22, 23]

Once large varices have developed, there is no need for further follow-up endoscopy; at this stage the patients should be treated to prevent bleeding. The prevalence of large varices is only about 9- 36% in non bleeders. These recommendations imply a considerable burden of endoscopies and related costs; they require that patients repeatedly undergo an unpleasant procedure, even though up to 50% of them may still not have developed esophageal varices 10 years after the diagnosis of cirrhosis.[24] .

Therefore, these guidelines might not be ideal for clinical practice. This inference is supported by recent studies from the United States and Italysuggesting that the guidelines are not being fully adopted. [25, 26] . Moreover, the guidelines were based largely on studies of patients with cirrhosis due to viral hepatitis or alcohol abuse; accordingly, it is unclear to what extent the guidelines may apply to patients with other causes of portal hypertension.

To reduce the number of unnecessary endoscopies in patients with cirrhosis but without varices, several studies have evaluated possible noninvasive markers of esophageal varices in patients with cirrhosis.[27-33] . The conclusion from most of these studies is that by selecting patients for endoscopic screening based on a few laboratory and/or ultrasonographic variables , usually the platelet count and the diameter of the portal vein , an appreciable number of endoscopies may be avoided, while keeping the rate of undiagnosed varices, which are at risk of bleeding, acceptably low . However, the predictive accuracy of such noninvasive markers is still considered to be unsatisfactory, and none of them has been recommended for use in clinical practice so far.[34] A recent inclusion in this scenario is the blood ammonia level predicts the

esophageal varices and large spontaneous porto systemic shunt presence. [30]

Studies combining venous ammonia and other non invasive predictors on Indian patients are limited . Such predictive factors may be expected to vary in different populations because of differences in the etiologies of liver cirrhosis, severity of liver disease. Therefore this study was conducted to evaluate the utility of blood ammonia, spleen size and platelet count as a predictor of esophageal varices and large spontaneous porto systemic shunt presence.

LITERATURE REVIEW

PORTAL HYPERTENSION

The natural history of cirrhosis can be divided into a preclinical phase and a subsequent clinical phase. The preclinical phase is usually prolonged over several years; once clinical events such as the development of ascites, encephalopathy, and variceal bleeding occur, the remaining course of the disease is much shorter and usually fatal. Portal hypertension is crucial in the transition from the preclinical to the clinical phase of cirrhosis ; it is a contributive mechanism of ascites and encephalopathy and a direct cause of variceal bleeding and bleeding-related death.

Portal hypertension in cirrhosis is determined by an increase in both intrahepatic vascular resistance and portal venous inflow. Intrahepatic vascular resistance is caused by the architectural distortion of the liver resulting from fibrosis and by increased sinusoidal tone. Portal venous inflow results from a combination of an hyper dynamic circulatory state and increased plasma volume. In response to the increased portal pressure, collateral circulation develops by the opening of preexisting vascular channels and possibly by neoformation of vessels. From a clinical standpoint, esophagogastric varices are the most important collateral

vessels: they tend to increase in size with the increase of portal pressure and rupture when wall tension exceeds a critical value.

Knowledge of the natural history of portal hypertension may help in making important decisions about the diagnosis, monitoring and follow-up, and treatment of patients with this condition.

Portal hypertension is classified accoding to the localization of the flow resistance as pre hepatic , intra hepatic and post hepatic blocks. The intra hepatic form is sub divided as presinusoidal , sinusoidal and post sinusoidal portal hypertension

NON – PARENCHYMATOUS PORTAL HYPERTENSION

1. PREHEPATIC PORTAL HYPERTENSION
2. INTRAHEPATIC PORTAL HYPERTENSION

A. PRESINUSOIDAL
   PARENCHYMATOUS PORTAL HYPERTENSION
B. SINUSOIDAL
C. POST SINUSOIDAL BLOCK

3. POST HEPATIC PORTAL HYPERTENSION

ESOPHAGEAL VARICES

Bleeding from ruptured esophagogastric varices is the most severe complication of cirrhosis and is the cause of death in about one third of cirrhotic patients. Varices form when the HVPG exceeds 10 mm Hg and usually do not bleed unless the hepatic venous pressure gradient (HVPG) exceeds 12 mm Hg [45]. Gastroesophageal varices have two main inflows, the first is the left gastric or coronary vein. The other major route of inflow is the splenic hilus, through the short gastric veins.

Four distinct zones of venous drainage at the gastroesophageal junction are particularly relevant to the formation of esophageal varices. The gastric zone, which extends for 2 to 3 cm below the gastroesophageal junction, comprises veins that are longitudinal and located in the submucosa and lamina propria. They come together at the upper end of the cardia of the stomach and drain into short gastric and left gastric veins. The palisade zone extends 2 to 3 cm proximal to the gastric zone into the lower esophagus. The perforating veins in the palisade zone do not communicate with periesophageal veins in the distal esophagus. The palisade zone is the dominant watershed area between the portal and systemic circulations. More proximal to the palisade zone in the esophagus is the perforating zone, where there is a network of veins. These veins are less likely to be

longitudinal and are termed perforating veins because they connect the veins in the esophageal submucosa and the external veins.

The truncal zone, the longest zone, is approximately 10 cm in length, located proximally to the perforating zone in the esophagus, and usually characterized by four longitudinal veins in the lamina propria. Veins in the palisade zone in the esophagus are most prone to bleeding because no perforating veins at this level connect the veins in the submucosa with the periesophageal veins. Varices in the truncal zone are unlikely to bleed. The periesophageal veins drain into the azygous system, and as a result, an increase in azygous blood flow is a hallmark of portal hypertension.

GASTRIC VARICES

The fundus of the stomach drains through short gastric veins into the splenic vein. In the presence of portal hypertension, varices may therefore form in the fundus of the stomach. Splenic vein thrombosis usually results in isolated gastric fundal varices. Because of the proximity of the splenic vein to the renal vein, spontaneous splenorenal shunts may develop and are more common in patients with gastric varices than in those with esophageal varices. The overall prevalence of gastric varices varies among studies, with figures ranging from 10% to more than 50%.[46,47.]

Gastric varices are classified according to sarin et al. [47] About 70% of the patients with gastric varices GOV 1, 21% had GOV 2, 6.7% had IGV 1 and 1.4% had IGV 2. Gastric varices are significantly more common in cirrhotic patients with a history of variceal bleeding than in those who have not bled, perhaps indicating that gastric varices develop at a more advanced stage of portal hypertension.Hemodynamic studies in patients with large gastric varices have demonstrated a lower portal pressure, large gastrorenal shunts, and less risk of hemorrhage but a somewhat greater likelihood of portosystemic encephalopathy. The overall incidence of bleeding from gastric varices is between 3% and 30%.[47].

Varices involving the fundus, were the cause of bleeding in 67% of all patients bleeding from gastric varices. Gastric varices tended to bleed less frequently but more severely than esophageal varices.

PORTAL HYPERTENSIVE GASTROPATHY

Portal hypertensive gastropathy (PHG) is a collective term that defines an array of diffuse macroscopic lesions observed in the gastric mucosa of patients with portal hypertension. A classification of this entity has been developed and its reproducibility has been thoroughly evaluated [48] .This classification distinguishes a mild form (when a mosaic like

pattern is present) and a severe form (when multiple red signs or black-brown spots are present).

The prevalence of PHG in reported series is extremely variable (7%–98%), The prevalence was relatively low (56%) in patients with a new diagnosis of cirrhosis, higher (75%) in patients with a previous diagnosis of cirrhosis and no prior bleeding, and even higher (91%) in patients with a previous variceal bleeding episode with current or prior sclerotherapy.

Thus, PHG shows a strong correlation with the duration of cirrhosis and the severity of portal hypertension, whereas the correlation with the degree of liver dysfunction is weak. The endoscopic appearance of PHG is stable in some patients and varies with time in most, showing steady deterioration or sustained improvement in about one fifth of the patients each, and fluctuations, with transition from mild to severe and vice-versa on sequential endoscopies, in about one fourth of patients. Bleeding from PHG can be acute or chronic. Endoscopically verified acute bleeding from PHG occurs in 2.5% of patients and chronic bleeding occurs in 12% of patients.

GASTRIC ANTRAL VASCULAR ECTASIA (GAVE)

GAVE ,also known as watermelon stomach is characterised by red patches or spots in either a diffuse or linear array in the antrum of the stomach , which can result in significant blood loss and leads to chronic iron deficiency anemia Its etiology is unclear. Vasoactive substances may play an important role in the etiology of vascular ectasia. Neuroendocrine cells containing vasoactive intestinal peptide and 5-hydroxtryptamine have been found close to the vessels in the lamina propria of resected specimens from GAVE patients .So, these mediators may be responsible for the vasodilatation and thus the propensity to bleed .GAVE in cirrhotic patients may be explained by the shunting of blood and altered metabolism of vasoactive substances in the presence of liver disease GAVE have several disease association as primary biliary cirrhosis , connective tissue disease etc. More than 70% of patients with GAVE syndrome do not have cirrhosis or portal hypertension .

In the setting of cirrhosis, GAVE syndrome can be difficult to differentiate from PHG. Both conditions are diagnosed endoscopically as collections of discrete red spots of ectatic vessels arranged in stripes along the antral rugal folds; however, the red spots of PHG appear in a background of mucosal mosaic appearance, but the mucosa underlying

GAVE is normal . Histologically , vascular ectasia in GAVE are seen in the mucosa associated with fibrin thrombi ,fibrohylinosis and spindle cell proliferation.

PORTAL HYPERTENSIVE INTESTINAL VASCULOPATHY

Portal hypertensive colopathy was defined endoscopically in patients with vascular ectasia, redness and blue vein .Vascular ectasia was further classified into two types: type 1, solitary vascular ectasia ; and type 2, diffuse vascular ectasia. As Child-Pugh class worsens and platelet count decreases, the prevalence of portal hypertensive colopathy increases in patients with liver cirrhosis. Colonoscopic examination is needed in these patients, especially those with worsening Child-Pugh class and decreasing platelet count, to prevent complications, such as lower gastrointestinal bleeding.

PORTAL HYPERTENSIVE ENTEROPATHY (PHE)

PHE is part of the spectrum of congestive gastroenteropathy .Its incidence doesn't correlate with the Child-Pugh score or with prior sclerotherapy. Circulating hormonal vasodilators from intestinal origin such as glucagon and nitric oxide elevate portal venous pressure aggravates noxious injury of the mucosa in rats with portal hypertension.

The important histologic features in the portal hypertensive patients include edema of the lamina propria, fibromuscular proliferation, a decreased villous/crypt ratio, and thickened muscularis mucosae.

The clinical implication of these changes is the increased chance of occult gastrointestinal blood loss. PHE is usually asymptomatic; massive hemorrhage has only rarely been described. The spectrum of portal hypertensive enteropathy varies from protein loosing enteropathy,altered intestinal motility, bacterial overgrowth and malabsorption and intestinal lymphagiectasia.

CLINICAL FEATURES OF PORTAL HYPERTENSION

SYMPTOMS

Hematemesis or melena (gastroesophageal variceal bleeding or bleeding from portal gastropathy) Mental status changes such as lethargy, increased irritability, and altered sleep patterns (presence of portosystemic encephalopathy)

Increasing abdominal girth (ascites formation)

Abdominal pain and fever (spontaneous bacterial peritonitis [SBP], which also presents without symptoms)

Hematochezia (bleeding from portal colopathy)

Physical examination

The signs of portosystemic collateral formation include the following:

Dilated veins in the anterior abdominal wall (umbilical epigastric vein shunts)

Venous pattern on the flanks (portal-parietal peritoneal shunting)

Caput medusa (tortuous collaterals around the umbilicus)

RECTAL HEMORRHOIDS

Ascites - Shifting dullness and fluid wave (if significant amount of ascitic fluid is present)

Paraumbilical hernia
Venous hum
Signs of liver disease include the following:
Ascites
Jaundice
Spider angiomas
Gynecomastia
Dupuytren contracture
Muscle wasting
Palmar erythema
Asterixis
Testicular atrophy
Splenomegaly

Hepatomegaly

Signs of hyperdynamic circulatory state include the following:

Bounding pulses

Warm, well-perfused extremities

Arterial hypotension

INVESTIGATION OF PORTAL HYPERTENSION

BLOOD INVESTIGATIONS

Liver function tests – to assess severity of the liver disease; reversal of albumin : globulin ratio indicates decompensation.

Prothrombin time - assess coagulation abnormality

Viral hepatitis serologies

Platelet count - value of < 150000/mm3 indicates thrombocytopenia.

Antinuclear antibody, antimitochondrial antibody, antismooth muscle antibody

Iron indices

Alpha1-antitrypsin deficiency

Ceruloplasmin, 24-hour urinary copper - To be considered only in individuals aged 3-40 years who have unexplained hepatic, neurologic, or psychiatric disease

IMAGING STUDIES

ULTRASONOGRAPHY

Ultrasound examination of the liver with Doppler study of the vessels has been used widely to assess patients with portal hypertension. Features suggestive of portal hypertension on ultrasonography include splenomegaly, portosystemic collateral vessels, reversal of the direction of flow in the portal vein (hepatofugal flow) , portal vein diameter greater than 11 mm and the absence of respiratory variations in the splenic and mesenteric veins.

Ultrasound examination can detect thrombosis of the portal vein, which appears as nonvisualization or cavernous transformation of the portal vein; the latter finding indicates an extensive collateral network in place of the portal vein. Splenic vein thrombosis also can be demonstrated.

PORTAL VEIN DOPPLER

Portal blood flow can be measured by Doppler ultrasonography, which is the easiest research method for detecting postprandial increases in splanchnic blood flow. Although Doppler ultrasonography is clinically useful in the initial evaluation of portal hypertension, the technique is not widely used to provide quantitative assessments of the degree of portal

hypertension. Pulsed Doppler Ultrasound was used to analyze hepatic artery wave forms near the porta hepatis.

The Resistive Index (RI) = [pcak systolic frequency shift (A) – minimum diastolic frequency shift (B)] / [peak systolic frequency shift (A)] has been calculated from this information. Using a cut off of greater than 0.77 this index has a sensitivity, specificity and overall accuracy of 68%, 70% and 69% respectively. portal blood flow velocity was found to correlate only with the presence and size of esophageal varices. The Congestion Index of the portal vein (derived from the ratio between the cross-sectional area of the portal vein and the mean velocity of portal flow) was significantly different in most clinical, biochemical and endoscopic subgroups and was correlated with liver function, presence and size of varices, and presence and degree of red signs.conjetion index of >0.1 are associated with portal hypertension with sensitivity and specificity of about 95%.

BARIUM STUDIES

Oesophageal varices appears as filling defects with a smooth contour in the lower third of the esophagus. Uphill and downhill varices can be clearly demonstrated with barium studies. Patients with portal hypertensive

gastropathy had thickened gastric folds, which had a mean thickness of 10 mm. The thickened folds had a nodular appearance with undulating contours and indistinct borders which is somewhat different from those of gastric varices, which classically appear as multiple rounded submucosal nodules or as serpentine folds in the gastric fundus.

COMPUTED TOMOGRAPHY

Computed tomography (CT) is useful for demonstrating many features of portal hypertension, including abnormal configuration of the liver, ascites, splenomegaly, and collateral vessels .Detection of varices may be an emerging indication for CT. Diagnosis of fundal varices by multidetector row CT (MDCT) is at least as accurate as endoscopic ultrasonography. CT is especially helpful in distinguishing submucosal from perigastric fundal varices and is considered a less invasive alternative to conventional angiographic portography in assessing portosystemic collaterals. At present, however, CT is not a recommended screening method for detecting large esophageal varices, but it may be a cost-effective method of screening for varices and preferred to endoscopy by patients.

MAGNETIC RESONANCE IMAGING

Gadolinium-enhanced magnetic resonance imaging can be used to measure and azygous blood flow, which is increased in patients with portal hypertension. MRI provides excellent detail of the vascular structures of the liver and can detect portal venous thrombosis and spleen stiffness in patients with portal hypertension, but the role of MRI in the assessment of portal hypertension requires further study. MRI can accurately assess the stiffness of even fatty livers.

ENDOSCOPIC ULTRASONOGRAPHY

Endoscopic ultrasound examination using radial or linear array ech endoscopes or endoscopic ultrasound mini-probes passed through the working channel of a diagnostic endoscope has been applied as an investigational tool in the evaluation of patients with varices. Cross-sectional area of varices to identify patients at increased risk of bleeding, size of and flow in the left gastric vein, azygous vein, and paraesophageal collaterals; changes after endoscopic therapy; and recurrence of esophageal varices following variceal ligation all can be assessed by endosonography. Endosonography can be combined with endoscopic measurement of transmural variceal pressure to allow estimation of variceal wall tension, which is a predictor of variceal bleeding

TRANSIENT ELASTOGRAPHY (FibroScan)

FibroScan (Transient Elastography) is a new device used to measure the elasticity or stiffness of the liver – the stiffer the liver, the more severe the hepatic fibrosis (scarring). It's extremely good at picking up mild or minimal disease, and very good at diagnosing cirrhosis, with 90-95% accurate positive predictive value, FibroScan also has other limitations that people wanting to undergo a FibroScan should be aware of; its inability to get an effective reading in patients with significant liver inflammation for those who have a pacemaker, or its inability to diagnose moderate fibrosis accurately, and its ineffectiveness in patients who are obese should all be noted.

ESOPHAGO GASTRO DUODENOSCOPY

Upper gastrointestinal endoscopy is the most commonly used method to detect varices. Endoscopic grading of esophageal varices is subjective. Various criteria have been used to try to standardize the reporting of esophageal varices. The best known of these criteria are those compiled by the Japanese Research Society for Portal Hypertension. The descriptors include red color signs, color of the varix, form (size) of the varix, and location of the varix. Red color signs include red "wale"

markings, which are longitudinal whip-like marks on the varix; cherry-red spots, which usually are 2 to 3 mm or less in diameter; hematocystic spots, which are blood-filled blisters 4 mm or greater in diameter; and diffuse redness. The color of the varix can be white or blue. The form of the varix at endoscopy is described most commonly.

Esophageal varices may be small and straight (grade I); tortuous and occupying less than one third of the esophageal lumen (grade II); or large and occupying more than one third of the esophageal lumen (grade III). Varices can be in the lower third, middle third, or upper third of the esophagus. Of all of the aforementioned descriptors, the size of the varices in the lower third of the esophagus is the most important. The size of the varices in the lower third of the esophagus is determined during withdrawal of the endoscope . Small varices, that is, those occupying less than one third of the lumen, are less than 5 mm in diameter, whereas large varices are greater than 5 mm in diameter.

Patients with large esophageal varices, Child (or Child-Pugh) class C cirrhosis (see later), and red color signs on varices have the highest risk of variceal bleeding within 1 year. Prophylactic treatment to prevent variceal bleeding is recommended in all patients with large esophageal varices irrespective of the presence or absence of red color signs .

ARTERIOGRAPHY

Injection of contrast medium into the speen either percutaneously or by laparoscopy ensures access to collaterals if radiological interventions are planned. Indirect splenoportography , hepatic vein phlebography, indirect mesentricoportography , transjugular and transhepatic splenoportography, umbilical vein portography are the some of the radiologic methods by which the collaterals can be ascertained.

MEASUREMENT OF PORTAL PRESSURE

Portal pressure can me measured either by direct or by indirect methods. Direct methods are invasive , cumbersome and rarely used. HVPG measurement , splenic pulp pressure measurement, variceal pressure , are the indirect methods. HVPG measurement is currently used to assess portal pressure.

The HVPG is the difference between the wedged hepatic venous pressure (WHVP) and free hepatic vein pressure (FHVP). It has been validated as the best predictor for the development of complications of portal hypertension.

Measurement of the HVPG requires passage of a catheter into the hepatic vein under radiologic guidance until the catheter can be passed no further, that is, until the catheter has been "wedged" in the hepatic vein. The catheter can be passed into the hepatic vein through the femoral vein or using a transjugular venous approach. HVPG is not effective for detecting presinusoidal causes of portal hypertension. HVPG is accurate for detecting only sinusoidal and postsinusoidal causes of portal hypertension.

The HVPG is measured at least three times to demonstrate that the values are reproducible. Measurement of the HVPG has been proposed for the following indications: (1) to monitor portal pressure in patients taking drugs used to prevent variceal bleeding; (2) as a prognostic marker (3) as an end- point in trials using pharmacologic agents for the treatment of portal hypertension; (4) to assess the risk of hepatic resection in patients with cirrhosis; and (5) to delineate the cause of portal hypertension . HVPG monitoring is not done routinely in clinical practice because no controlled trials have yet demonstrated its usefulness.

The development of gastroesophageal varices requires a portal pressure gradient of at least 10 mm Hg. Furthermore, a portal pressure gradient of at least 12 mm Hg is thought to be required for varices to

bleed; other local factors that increase variceal wall tension also are needed[77] because all patients with a portal pressure gradient of greater than 12 mm Hg do not necessarily bleed.

Factors that influence variceal wall tension can be viewed in the context of the law of Laplace:

$$T = PR / W$$

where T is variceal wall tension, P is the transmural pressure gradient between the variceal lumen and esophageal lumen, r is the variceal radius, and w is the variceal wall thickness. When the variceal wall thins and the varix increases in diameter and pressure, the tolerated wall tension is exceeded and the varix will rupture. These physiologic observations are manifested clinically by the observation that patients with larger varices (r) in sites of limited soft tissue support (w), with elevated portal pressure (P), tend to be at greatest risk for variceal rupture from variceal wall tension (T) that becomes excessive. One notable site in which soft tissue support is limited is at the gastroesophageal junction. The lack of tissue support and high vessel density may contribute to the greater frequency of bleeding from varices at the gastroesophageal junction.

The law of Laplace also has implications for the relevance of pharmacologic therapies aimed at reducing portal pressure. Reductions in portal pressure will reduce the variceal transmural pressure gradient, thereby reducing the risk that variceal wall tension will become excessive and varices will rupture. Clinically, a reduction in the hepatic venous pressure gradient to less than 12 mm Hg almost negates the risk of variceal hemorrhage. The changes in portal pressure and local variceal factors, however, are dynamic and influenced by a number of physiologic (an increase in intra-abdominal pressure, meal-induced increases in portal pressure), diurnal (circadian changes in portal pressure), and pathophysiologic (acute alcohol use) factors, and portal pressure and esophageal variceal pressure may vary at different times.

AIM AND OBJECTIVES OF THE STUDY

1. To investigate the diagnostic utility of venous ammonia levels, spleen size and platelet count as non-invasive markers of esophageal varices.

2. To correlate these markers with endoscopy findings, ultra sound features and Child- Pugh classification as indices of shunt presence.

3. To evaluate non – invasive markers in predicting large esophageal varices.

4. To evaluate non – invasive markers in predicting Gastric varices and large porto systemic collaterals .

METHODS

The study included consecutive patients with liver cirrhosis admitted in our institution (Department of Digestive Health and Diseases , Government Peripheral Hospital , Anna nagar , Chennai -102) which is a major tertiary care centre for liver diseases . Ethical Committee approval was obtained for this study design. Patients were included in this study after their willingness to undergo necessary investigations . Informed written consent was taken before the enrolment in this study.The period of study is from December 2008 to January 2011.

Inclusion criteria :

1.Cirrhosis with portal hypertension

EXCLUSION CRITERIA :

1. Previous history of EST / EVL / Porto systemic shunt surgery
2. Patients on drugs as a primary prophylaxis for varices
3. Past history of variceal bleeding
4. Hepato cellular carcinoma , detected by ultrasound
5. Severe co-morbid illness precluding upper GI scopy
6. History of drug usage which increases blood ammonia level
7. Intravenous drug abusers

8. Acute or chronic renal failure

CLINICAL EVALUATION:

In all the patients, the diagnosis of cirrhosis with portal hypertension was established by detailed clinical (spider nevi, organomegaly) etiological (significant alcohol intake , blood transfusion, tattooing, high risk behaviour etc.) , radiological (portal vein, spleen size) Ascites was graded as none, mild (detectable only on ultrasound), moderate (visible moderate symmetrical abdominal distension) or severe (marked abdominal distension)[38] . Hepatic encephalopathy was graded from grade 0 to IV, as per west Heaven criteria.

BLOOD INVESTIGATIONS :

Includes haemoglobin , WBC count , platelet count , prothrombin time , bilirubin (total , direct, indirect), total protein albumin and globulin , alanine amino transferase , aspartate amino transferase, HBsAg and Anti HCV. Tests for auto immune liver disease, haemochromatosis and Wilson disease were done only if clinical situation warrents the study.

ULTRASOUND ABDOMEN :

The non-invasive assessment of liver cirrhosis was performed to all patients by radiologists on the basis of US/US-doppler examinations (coarse echo-texture, nodularity presence, increased caudate/right lobe ratio, hypertrophy of the left lobe, characterized by a rounded inferior marginal edge,)

Spleen measurements of Spleen Longitudinal Diameter (SLD) were performed by postero-lateral scanning with the probe footprint aligned along an intercostals space to provide a longitudinal view of the spleen. The patients were asked to breathe slowly, taking long breaths – as varying degrees of inspiration and expiration are needed to optimize splenic visualization – and to roll on the right side to some extent to aid visualization. At this point, the maximum length, i.e., the optically greatest overall longitudinal dimension obtained from one of the two poles was recorded. Given the high variability in detecting spleen measurements, an US value ≥ 110 mm was chosen to correspond to splenomegaly.

ASCITES PRESENCE

When a patient is in a supine position, free fluid tends to accumulate in the flanks, particularly the superior end of the right paracolic gutter, and

in the pelvis due to the effects of gravity. These areas were carefully assessed. Small quantities were sought for around the liver or spleen surface and in the Morrison's pouch. [26]

PORTAL VEIN DOPPLER

Umbilical vein patency, i.e. diameter ≥ 3 mm, was easily detected within the echogenic ligamentum teres hepatis and was confirmed by color Doppler US. SRS was detected by the same method. The direction of blood flow in the collateral vein was also analyzed in each patient. The Doppler angle used to examine the portal vein was less than 50° in all examinations.

Portal vein enlargement with decreased flow velocity, absence of a normal doppler waveform, hepatofugal flow). No evidence of hepatocellular carcinoma at the first hepatic decompensation was detected. Renal insufficiency was properly excluded.

ENDOSCOPIC FEATURES

ESOPHAGEAL VARICES

Esophageal varices were graded according to paquet grading system. It grades esophageal varices from I – IV. Patient were further classified as

small varices (paquet's grade I,II), large varices (paquet's grade III , IV).[40]

PORTAL HYPERTENSIVE GASTROPATHY

PHG was assessed according to the NIEC classification .[41] Mosaic-like pattern was characterized by the presence of small, polygonal areas surrounded by a whitish-yellow depressed border. Red-point lesions were small, flat, lesions (1 mm in diameter). Cherry-red spots were red-coloured, round lesions, slightly protruding into the lumen of the stomach, (2 mm in diameter). Black- brown spots were irregularly shaped flat spots, black or brown, persistently present after washing.

Ano-rectal varices and Portal Hypertensive Colopathy

For ethical reasons, only patients who presented with a history of hematochezia at entry underwent colonoscopy to track ano-rectal varices to differentiate from haemorroides.Portal hypertensive colopathy was defined endoscopically in patients withvascular ectasia (solitary or diffuse), redness, and blue vein[42]

Hepatic encephalopathy grade

Hepatic encephalopathy was graded based on the level of consciousness, intellectual functions, behaviour and neuromuscular functions according to West Haven (W-H) criteria .W-H grade 0 encephalopathy was ascertained as previously described. [42,43.]

Venous ammonia concentration

Venous ammonia levels were quantified according to enzymatic determination with glutamate dehydrogenase using rapid and interference-free photometry (340 nm), and were expressed as μ mol / L.Due to reasons of safety, blood was kept chilled and immediately sent to the laboratory for determination. Normal value is between 11- 35μ mol / L.

STATISTICAL ANALYSIS

The chi square was used to look for significance of each variables in predicting esophageal , gastric and other large porto systemic collaterals. When confronted with the question of how accurate a parameter was in identifying portosystemic collateral veins presence, the discrimination with relative cut-off or criterion was evaluated using .Sensitivity (true positive rate), specificity (true negative rate) were also weighted for the same purpose. Optimal cut-off was considered the threshold value with the best specificity/sensitivity.

To predict the presence of portosystemic collateral veins, hepatic decompesation and ascites presence the logistic regression (Enter Method) was employed utilizing as independent variables US values for SLD, platelets count and blood NH4 concentrations. The same tool was carried out to predict the large (II and III grade) EV presence by NH4 concentrations.

RESULTS

Patient characteristics

A total of 61 patients were included in the study. Of those, 43(70.5%) were male and 18 were female (29.5%). The symptom patient duration in half of the patients falls between 90 – 180 days . Ascites was clinically present in 77% of patients. Pedal edema was present in 44% of patients. About 37 patients had jaundice at presentation. Spleen was palpable in 44 % of patients.

The demographic and clinical characteristics of the patients are presented in Table 1.

TABLE 1 : DEMOGRAPHIC CHARECTERISTICS OF STUDY PATIENTS

Sex	Frequency	Percent
Male	43	70.5
Female	18	29.5
Total	61	100.0

TABLE 2 : FREQUENCY OF ASCITES IN STUDY POPULATION

ASCITES	Frequency	Percent
Absent	14	23.0
Present	47	77.0
Total	61	100.0

TABLE 3 : PALPABLE SPLEEN

Spleen	Frequency	Percent
0	34	55.7
1	27	44.3
Total	61	100.0

0 – present ; 1- absent

The majority of the patients were Child-Pugh class C , 29 (47.5%). Patients with child A and B constitutes 14 (23%) & 18 (29.5%) respectively. Ascites was found in 77 % of the patients by ultrasonography and clinical examination.

TABLE 4 : CHILD PUGH CLASS IN STUDY POPULATION

CTP SCORE	Frequency	Percent
A	14	23.0
B	18	29.5
C	29	47.5
Total	61	100.0

Esophageal varices were present in 37 patients of which 11 had small varices (18%) and 26 (42.6%) had large varices . Gastric varices was present only in 9 patients.

TABLE 5 : FREQUENCY OF ESOPHAGEAL VARICES IN STUDY GROUP

EV	Frequency	Percent	Valid Percent	Cumulative Percent
Absent	24	39.3	39.3	39.3
Small	11	18.0	18.0	57.4
Large	26	42.6	42.6	100.0
Total	61	100.0	100.0	

EV – Esophageal Varices

TABLE 6 : FREQUENCY OF GASTRIC VARICES

Gastric Varices	Frequency	Percent	Valid Percent	Cumulative Percent
Absent	55	90.2	90.2	90.2
Present	6	9.8	9.8	100.0
Total	61	100.0	100.0	

20 patients had (32.8%) portal hypertensive gastropathy along with esophageal varices

TABLE 7 : FREQUENCY OF PORTAL HYPERTENSIVE GASTROPATHY

PHG	Frequency	Percent	Valid Percent	Cumulative Percent
Absent	41	67.2	67.2	67.2
Present	20	32.8	32.8	100.0
Total	61	100.0	100.0	

Large spontaneous porto systemic shunts were detected by color dopper in 4 patients .

TABLE 8 : FREQUENCY OF LARGE SPONTANEOUS SHUNTS (LSS)

LSS	Frequency	Percent
Absent	51	83.6
Present	10	16.3
Total	61	100.0

The majority of patients in this study were belong to alcoholic cirrhosis which constitutes of about 60.7%. , which is followed by Hepatitis B , 19.7%

TABLE 9: ETIOLGY OF CIRRHOSIS

Etiology	Frequency	Percent	Valid Percent	Cumulative Percent
AIH	1	1.6	1.6	1.6
ALC	37	60.7	60.7	62.3
CRYP	6	9.8	9.8	72.1
HBV	12	19.7	19.7	91.8
HCV	5	8.2	8.2	100.0
Total	61	100.0	100.0	

Variables associated with the presence of oesophageal varices on univariate analysis Eleven variables considered relevant to the presence of oesophageal varices were tested using univariate analysis. Results are summarized in Table 5.

TABLE 10 : DESCRIPTIVE STATISTICS OF VARIABLES ASSOCIATED WITH PRESENCE OF ESOPHAGEAL VARICES

Variables	N	Minimum	Maximum	Mean	Std. Deviation
(DD) DISEASE DURATION	61	20	240	85.98	46.982
Platelets	61	70000	415000	168049.18	78614.974
Bilirubin	61	.8	11.2	2.495	1.6767
SAAG	61	.9	1.6	1.231	.1478
PLT/SLD RATIO	61	236.92	3365.38	1367.5889	739.54224
SPLEEN SIZE	61	9.0	26.0	13.264	3.3378
(PV) PORTAL VEIN DIAMETER	61	8	18	12.26	2.352
(SV) SPLENIC VEIN DIAMETER	61	7	12	8.54	1.478
Coloumn	61	1	4	3.03	.983
Length	61	1	12	8.02	2.102
NH_4	61	38	108	72.49	19.607

PLD/SLD – Platelet- Spleen ratio

Univariate analysis revealed that platelet count, spleen width, portal diameter CTP grade were significantly associated with the presence of oesophageal varices

VARIABLES PREDICTING PRESENCE OF ESOPHAGEAL VARICES (EV)

Platelet count of 1,50,000 /mm^3 was considered as thrombocytopenia and it correlate well with the presence of esophageal varices.

TABLE 11 : PLATELET COUNT PREDICTING EV

Platelets	GRADE		Total
	small	large	
<1,50,000	7	20	27
> 1,50,000	17	17	34
Total	24	37	61

P values 0.05

A Platelet / spleen ratio of about 909 was chosen as a cut off value according to previous studies .

TABLE 12 : PLATELET/ SPLEEN RATIO PREDICTS EV

PLD/SLD	EV		Total
	small	large	
<909	21	17	38
>909	3	20	23
Total	24	37	61

P value .001

Spleen size is another important predictor of esophageal varices. Spleen size of more than 11cms was chosen as acut off value.

TABLE 13 : Spleen size as a predictor of EV

SPLEEN	GRADE		Total
	small	large	
>11 cm	9	30	39
<11 cm	15	7	22
Total	24	37	61

P value .001

TABLE 14 : Portal vein size size correlating with EV presence

Portal vein	Grade			Total
	Absent	Small	Large	
< 11 mm	19	7	11	37
>11 mm	5	4	15	24

P- value 0.02

TABLE 15 : CTP grade correlates with the presence of varices.

EV		CTP			Total
		A	B	C	
Absent	Count	9	6	9	24
Small	Count	2	7	2	11
Large	Count	3	5	18	26

P value 0.006

Normal Venous ammonia level is between 10–35 μmol/L.Values more than 35 was considered abnormal

TABLE 16 : VENOUS AMMONIA LEVEL

NH3	EV		TOTAL
	present	Absent	
>35mmol	33	17	50
<35 mmol	4	7	11
Total	24	37	61

P value < 0.05

Data showing Association of non Invasive markers with collaterals other then EV

Variable	GV (P value)	(LSS) P value	PHG (P value)
NH_4	0.7	0.4	0.1
Spleen size	0.2	0.2	0.1
Platelet count	0.04	0.02	0.02

The above data shows only platelet count has got association with collaterals other then EV

DISCUSSION

With the growing number of chronic liver disease in the world , the likelyhood of patients undergoing variceal screeing by endoscopy will also increase. Non invasive screening for identifying patients with high risk varices will definetly of help by means of reducing the cost and improve patient's tolerability Studies conducted on non invasive predictor of varices (Table -17) lack uniformity in their structure . The conclusion from most of these studies is that by selecting patients for endoscopic screening based on a few laboratory and/or ultrasonographic variables (usually the platelet count and the diameter of the portal vein), an appreciable number of endoscopies may be avoided, while keeping the rate of undiagnosed varices, which are at risk of bleeding, acceptably low .However, the predictive accuracy of such noninvasive markers is still considered to be unsatisfactory, and none of them has been recommended for use in clinical practice so far.45

Practice guidelines for the treatment of portal hypertension recommended endoscopic screening of patients with cirrhosis for varices, and treatment of patients with medium or large varices to prevent bleeding. These recommendations imply a considerable burden of endoscopies and related costs; patients repeatedly undergo an unpleasant

procedure, even though up to 50% of them may still not have developed esophageal varices 10 years after the diagnosis of cirrhosis.

Cirrhosis is the most advanced form of liver disease and variceal hemorrhage is one of its lethal complications. Over half of the patients with cirrhosis will develop varices. The risk of bleeding once OV formed is 20% to 35% within 2 years.[49] The reported mortality rate from first episode of variceal bleeding is 17% to 57%. Of those who survive the initial episode of bleeding and who do not receive active treatment, the risk of recurrent bleeding is approximately 66% and usually occurs within 6 months of the initial bleeding episode.[(50)]

Because cirrhotic patients with large esophageal varices are at a high risk for bleeding, preventive efforts have concentrated on identifying cirrhotic patients with large varices. [51] In 1997, The American Collage of Gastroenterology (ACG) recommended screening endoscopy for cases with established cirrhosis who were candidates for medical therapy [52] . AASLD recommended screening endoscopy for varices and to be in particular routine in child class B and C patients, but in child class A to be limited to patients with evidence of portal hypertension[53]

It was estimated that 100 screening endoscopy need to be preformed to prevent 1-2 cases of variceal bleeding .Therefore, identification of clinical features that can accurately predict esophageal varices and help

identifying patients at greatest risk is important to improve the yield and cost- effectiveness of endoscopic screening.

Bleeding occurs in significant proportion of patients with severe PHG which accounts for most non variceal bleeding episodes in patients with cirrhosis and portal hypertension. PHG bleeding is a serious complication, which is usually chronic and insidious but occasionally massive and life – threatening[54] .Overt hemorrhage from the gastric mucosa occurred in 60% of patients with severe PHG with a cumulative risk of bleeding of 75% over a 5 –year follow –up period [55]

In the present study, the parameters linked to portal hypertension (platelet count, portal vein diameter, splenic diameter and platelet count/spleen ratio), were associated with the presence of esophageal varices. The issue of identifying patients with EV at risk of bleeding by non invasive means is relevant and has been addressed in several recent studies [67,] but only few Indian studies compared the above parameters as a prediction of gastric varices and other large porto systemic collaterals. This study is an attempt to achieve this goal

Commenting on the results, our data in cirrhotic patients support a good association between blood NH_4 levels and EV presence. The blood ammonia determination suffers from some limits in its measurements. In

fact, the collection, handling, storage, and analysis of blood samples are all potential sources of error. Recommendations has to be made on the collection and processing of blood samples, for it is bystandardization and rigid adherence to these techniques that the reliability of the test results will be improved.

Our data in this study agree with the body of present knowledge. When comparing the performance of blood ammonia with the PLTs/SLD ratio [(56)] the only marker contextually studied, we found a not so much dissimilar reliability. The advantages of the PLTs/SLD ratio are evident because they do not suffer from external confounding factors. The disadvantages are consistent with the fact that thrombocytemia is sometime related to the auto-antibodies presence that turns out in falsely low count of PLTs. Indeed, the opposite, falsely high count of PLTs, could be detected in patients suffering from liver cirrhosis with hepatocarcinoma.

The key point is not whether to recommend endoscopy or not but when to undergo it. Decision about the optimal intervals for surveillance mainly to detect large varices depends on what proportion of patients that bleeds before starting prophylactic treatment we are willing to accept. According to this study patients with high levels of NH_4 should undergo endoscopy faster[81].

In determining portal hypertension,mechanisms potentially reversible are involved, i.e., contractility of sinusoidallining cells, systemic mediators of arteriolar resistance, production ofendothelins or nitric oxide, and swelling of hepatocytes [57] However, other irreversible factors such as tissue fibrosis and regeneration increase resistance in the sinusoids and terminal portal venules, playing a key role. Even though PHG is recognized as a clinical entity associated to portal hypertension, its significance has not yet been elucidated [30]

Our observation that blood NH_4 levels predicted both ascites and collaterals presence is intriguing, reinforcing the concept of a common origin. Data from long follow-up of patients suffering from compensated cirrhosis B show that poor hepatic reserve and severity of portal hypertension significantly correlate [59] At the same manner, measurements of portal pressure provide unique prognostic information for predicting portal hypertensive-related bleeding and mortality in patients with alcoholic cirrhosis [60] also in patients without clear presence of EV [(31)]

High values of blood NH_4 are important because they point out an incoming liver decompesation; in fact, less blood reaches the liver, diminishing thus the hepatic reserve. Portal-systemic collaterals provide a

pathophysiological route to decompress the hypertensive portal system. Despite this, the vascular resistance of the collateral bed is still greater than the resistance of the liver, and portal pressure does not decrease [62] .What is more, ammonium compounds increase vascular tone by causing influx of extracellular calcium through the voltage-dependent calcium channel and intracellular alkalinisation [63]

While determining indirect evidence of portosystemic shunts presence, some laboratory parameters have already been proposed, i.e., Serum Bile Acids (SBA) and Indocyanine Green Clearance (IGC). Both are reliable, butblood ammonia level is a higher sensitive and specific parameter [64]

Colonoscopy was not offered to any patient as none of the patients have symptoms of portal hypertensive colopathy. Although detection of other portosystemic collaterals besides EV improves the specificity of NH4, it is barely important in clinical practice as prophylactic remedies are not warranted.

Platelet count

Thrombocytopenia in patients with cirrhosis has historically been attributed to hypersplenism due to portal hypertension. Several studies

suggest that platelet count may predict the presence of EV in patients with cirrhosis . However, the discriminating threshold for the presence of varices varies widely, ranging between 68,000 and 160,000/mm^3 [65] . The sensitivities for thrombocytopenia fluctuate from 62% to 100%, and the specificities range from 18% to 77% [66] .Our data suggest that the multivariate analysis failed to show any significant difference between thrombocytopenia and the risk of EV. In addition, platelet count might not be an ideal predictor of the presence of EV in HBV-related cirrhosis. A possible explanation is that other factors, such as suppressive effects of viruses on bone marrow and antibody-mediated destruction of platelets, may play a more important role in HBV-related cirrhosis than that in alcohol cirrhosis, in addition to decreased thrombopoeitin and interleukin-11 [67] .

STUDIES ON PLATELET COUNT

According to **Zaman et al** , Platelet count <88,000 was the only parameter identified by univariate/multivariate analysis ($p < 0.05$) as associated with the presence of large esophageal varices[68]

Thomopoulous et al in his study , Seventeen variables considered relevant to the prevalence of oesophageal varices . Oesophageal varices

were present in 92 patients (50%), and large varices in 33 patients (17.9%).[69]

Factors independently associated with the presence of large oesophageal varices on multivariate analysis were platelet count, size of spleen and presence of ascites by ultrasound.

In **Chalasani et at** [70] , a study on three hundred and fourty patients , the prevalence of large esophageal varices was 20%. On multivariate analysis, splenomegaly ,detected by computed tomographic scan (odds ratio: 4.3; 95% confidence interval: 1.6-11.5) or by physical examination (odds ratio: 2.0; 95% confidence interval: 1.1-3.8), and low platelet count were independent predictors of large esophageal varices. On the basis of these variables, cirrhotics were stratified into high- and low-risk groups for the presence of large esophageal varices. Patients with a platelet count of $\geq$ 88,000/mm3 (median value) and no splenomegaly by physical examination had a risk of large esophageal varices of 7.2%. Those with splenomegaly or platelet count < 88,000/mm3 had a risk of large esophageal varices of 28% ($p < 0.0001$).

SPLENOMEGALY

Splenomegaly is recognized as one of the diagnostic signs of cirrhosis and portal hypertension. Our data showed that spleen width measured by ultrasonography was an independent predictor for the presence of varices.

Dib N, et al[71] identified non invasive diagnosis of large esophageal varices because of prognostic and economic issues. Indirect echographic markers of portal hypertension and esophageal varices (ascites, portal vein diameter > or = 13 mm, spleen length, maximal and mean velocimetry of portal vein flow, respectively < 20 cm/s and < 12 cm/s) could be useful. Among this parameters, spleen length is an independent predictive marker of esophageal varices

In **Sharma et al** [72] study, 101 patients (median age 45; range 15-74 years; 87 male; Child-Pugh class: A 18, B 31, C 52), 46 had LEVx. On univariate analysis, five variables were significantly associated with the presence of LEVx.

These included pallor (P = 0.026), palpable spleen (P = 0.009), platelet count (P < 0.002), total leukocyte count (P < 0.0004) and liver span on ultrasound (P = 0.031). On multivariate analysis, two of these

parameters, namely low platelet count and presence of palpable spleen, were found to be independent predictors of the presence of LEVx.

In **Jeon sw et al** study [73] variables associated with the presence of esophageal varices on univariate analysis were serum albumin, total bilirubin, prothrombin time and platelet count ($P < 0.05$). On multivariate analysis, independent variables were platelet count (odds ratio (OR) 0.922; 95% confidence interval (CI), 0.86-0.99), diameter of spleen (OR 5.4; 95% CI, 1.63-17.88) and platelet count/spleen diameter ratio (OR 1.007; 95% CI, 1.01-1.02). The optimal critical value for the diameter of spleen was 11 cm. The sensitivity and specificity with this value were 84% and 63%, respectively

Platelet count/ spleen ratio

With the best cut-off value of 909 , the platelet count/spleen width ratio yielded a low diagnostic accuracy of 60.3%, which suggests that it is not an ideal predictor for EV.

In a study conducted by **Schwarzenberger et al** [74] of the 137 patients with 87 (63.5%) men and a mean age of 56 years, seventy-six (55%) patients had esophageal varices.Using a platelet count/spleen diameter ratio with a cut-off value of 909, yielded a negative predictive value of only 73% and a positive predictive value of 74%.

Giannini E et al [75] conducted a study in 121 patients, ultrasonographic measurement of spleen bipolar diameter. Platelet count/spleen diameter ratio were calculated for all patients. The prevalence rates of OV were 61% and 58% in the first and second groups of patients, respectively.the platelet count/spleen diameter ratio was the only parameter which was independently associated with the presence of OV in a multivariate analysis. A platelet count/spleen diameter ratio cut off value of 909 had 100% negative predictive value for a diagnosis of OV. This result was reproduced in the second group of patients as well as in patients with compensated disease. In a cost-benefit analysis, screening cirrhotic patients according to the "**platelet count/spleen diameter ratio strategy" was far more cost effective compared with the "scope all strategy**".

In **Baig WW et al** [76] study, the platelet count to spleen diameter ratio had the highest accuracy among the three parameters. By applying receiver operating characteristic curves, a platelet count to spleen diameter ratio cut-off value of 1014 was obtained, which gave positive and negative predictive values of 95.4% and 95.1%, respectively.

In **Zaman et al** study[77] , A total of 218 cirrhotic patients underwent screening endoscopy for EV. Platelet count/spleen diameter ratio was assessed in all patients and its diagnostic accuracy was calculated. Prevalence of EV was 54.1%. The platelet count/spleen diameter ratio had 86.0% (95% CI, 80.7- 90.4%) diagnostic accuracy for EV, which was significantly greater as compared with either accuracy of platelet count alone (83.6%, 95% CI 78.0- 88.3%, P= 0.038) or spleen diameter alone (80.2%, 95% CI 74.3-85.3%, P= 0.018). The 909 cutoff had 91.5% sensitivity (95% CI 85.0-95.9%), 67.0% specificity (95% CI 56.9-76.1%), 76.6% positive predictive value, 87.0% negative predictive value, 2.77 positive likelihood ratio, and 0.13 negative likelihood ratio for the diagnosis of EV. Accuracy of the platelet count/spleen diameter ratio was maintained for both severity and etiology of disease subgroups.

Studies on other non invasive markers

According to **Bressler B et al** [78] , a total of 235 patients with chronic liver disease, including 79 patients with PBC,7 patients with PSC , 104 patients with chronic viral hepatitis, and 45 with non-alcoholic cirrhosis of differing aetiologies, oesophageal varices were detected in 26 (30%) of the PBC/PSC group, 38 (37%) of the viral hepatitis group, and 21 (47%) of the "other" group. Applying multiple logistic regression analysis to the data in the group with PBC/PSC, platelets <200,000/mm3 (odds ratio (OR) 5.85 (95% confidence interval (CI) 1.79-19.23)), albumin <40 g/l (OR 6.02 (95% CI 1.78-20.41)), and serum bilirubin >20 micromol/l (OR 3.66 (95% CI 1.07-12.47)) were shown to be independent risk factors for oesophageal varices. The study conclude patients with a platelet count <200,000/mm3, an albumin level <40 g/l, and a bilirubin level >20 micromol/l should be screened for oesophageal varices.

Ng fh[79] on prediction of esophageal varices conclude that **Endoscopic screening for EGV was not necessary until thrombocytopenia or ascites occurred.** In their study, ninety-two patients were recruited. From all patients studied, the size of palpable spleen, liver chemistry value, platelet count, prothrombin time, diameter of main portal vein and splenic length . Low platelet count and presence of

ascites were the significant independent predictors for high-grade EGV (concordance rate 0.83). The optimal critical value for the platelet count was 150 x 10(9)/L. Of patients without thrombocytopenia and ascites, 37% had low-grade EGV but none had high-grade EGV, whereas 38 and 35% of patients with thrombocytopenia or ascites had low and high-grade EGV, respectively. Therefore, this predictive model for high-grade varices had a positive and negative predictive value of 35 and 100%, respectively.

In **Madhotra et al study**[80] , independent predictors of large varices were thrombocytopenia (p = 0.02) and splenomegaly (p = 0.04) seen using imaging. A platelet count of less than 68,000/mm ^{3} had the highest discriminative value for large EV with a sensitivity of 71% and a specificity of 73%. Splenomegaly had sensitivity and specificity of 75% and 58%, respectively None of the parameters , namely platelet count , spleen size , platelet /spleen size ratio and venous ammonia level correlate with the presence of gastric varices. Similarly none of these parameters correlate with the large porto systemic shunts .

CONCLUSION

1. Identifying high ammonia levels in cirrhotic patients is a good non invasive marker of esophageal varices

2. Among the non invasive markers studied, only platelet count predicts Gastric varices, portal hypertensive gastropathy and large spontaneous shunts.

3. Spleen size & portal vein size are sonographic markers of large esophageal varices

4. Simple platelet / spleen ratio is a useful predictor of large esophageal varices

5. Non invasive predictors are safe, acceptable, patient friendly method of identifying esophageal varices

6. Non Invasive markers are helpful in selecting patients with low probability of esophageal varices in whom upper GI endoscopy may not be needed.

Fig 1 : Sex Ratio

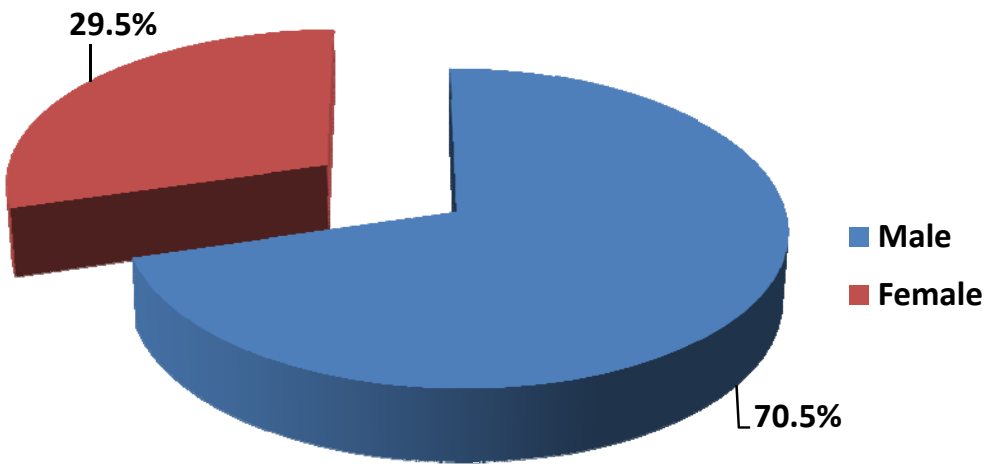
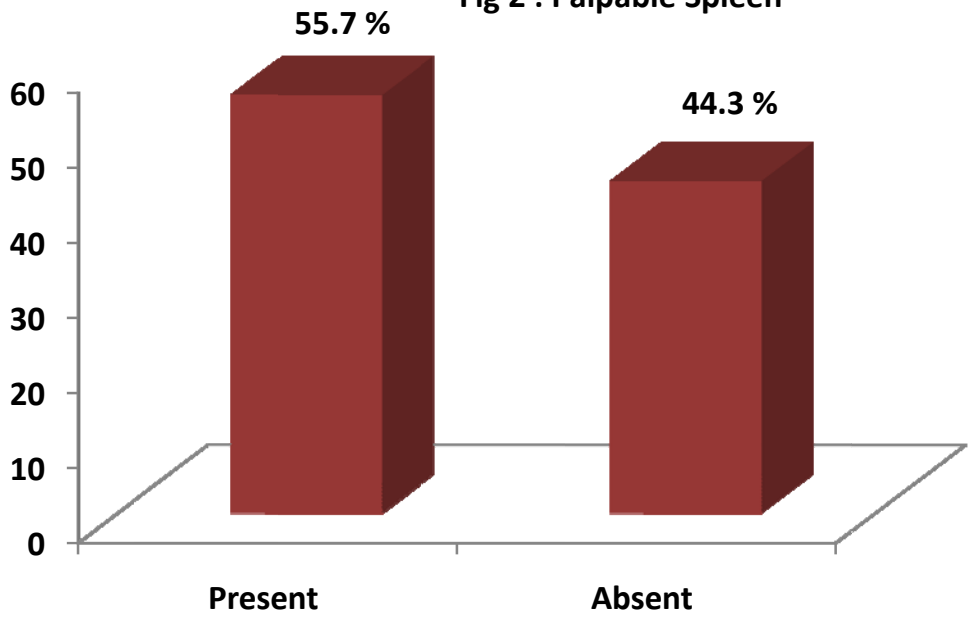


Fig 2 : Palpable Spleen



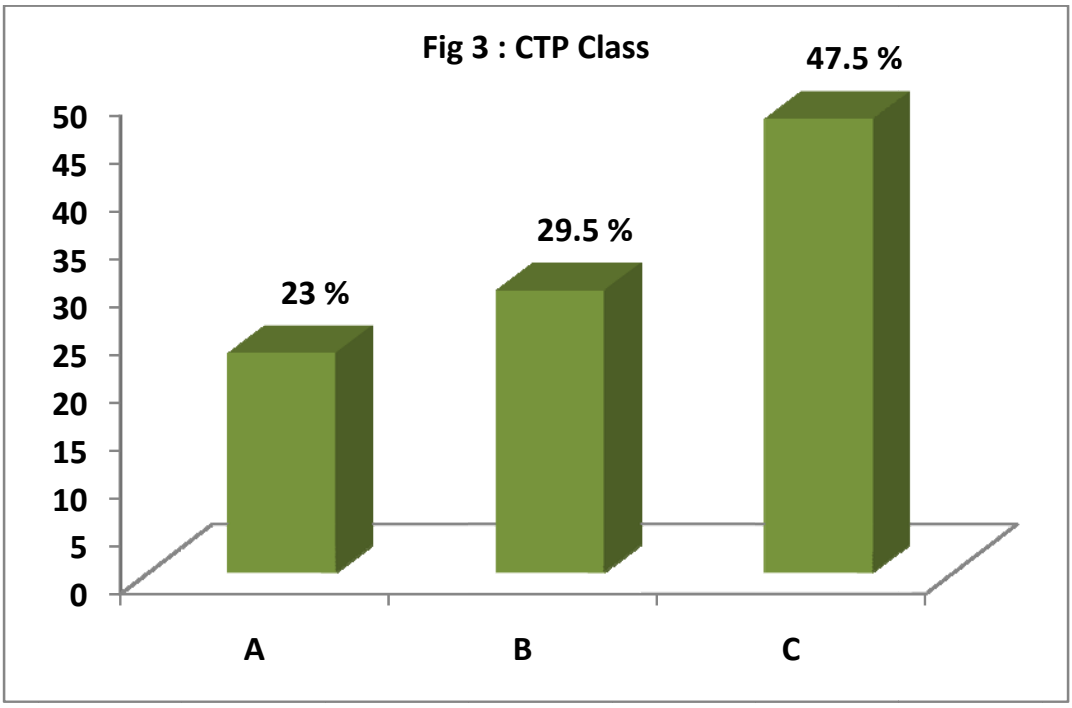


Fig 3 : CTP Class
47.5 %
29.5 %
23 %
50
45
40
35
30
25
20
15
10
5
0
A
B
C

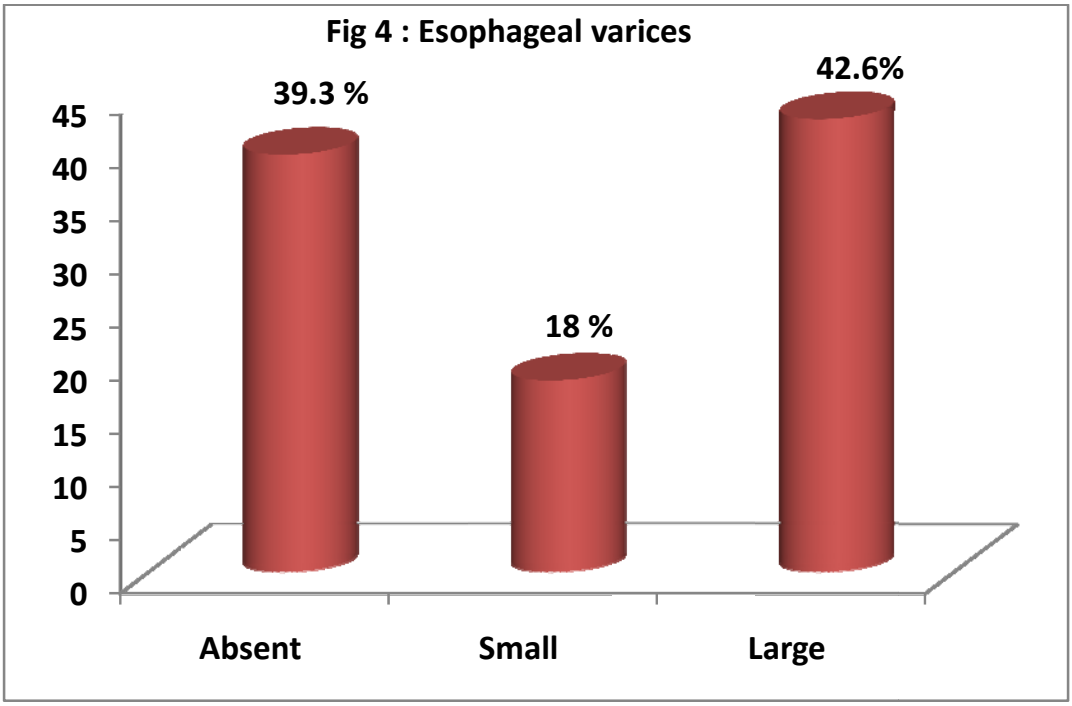


Fig 4 : Esophageal varices
42.6%
39.3 %
18 %
45
40
35
30
25
20
15
10
5
0
Absent
Small
Large

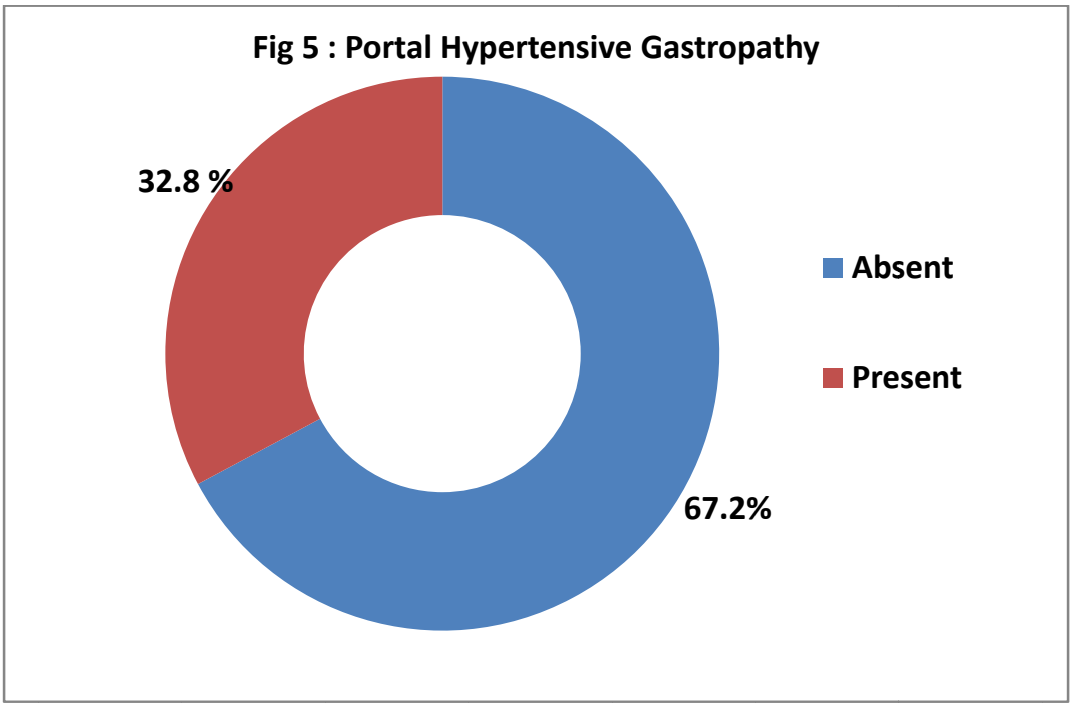


Fig 5 : Portal Hypertensive Gastropathy
32.8 %
67.2%
Absent
Present

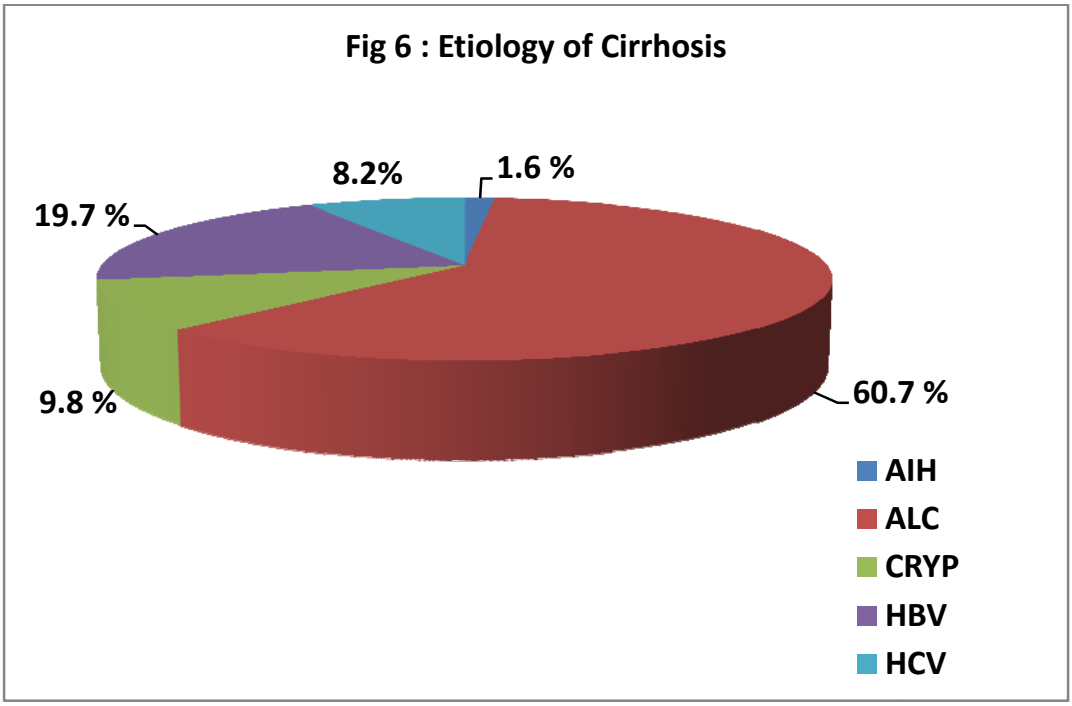


Fig 6 : Etiology of Cirrhosis
8.2%
1.6 %
19.7 %
9.8 %
60.7 %
AIH
ALC
CRYP
HBV
HCV

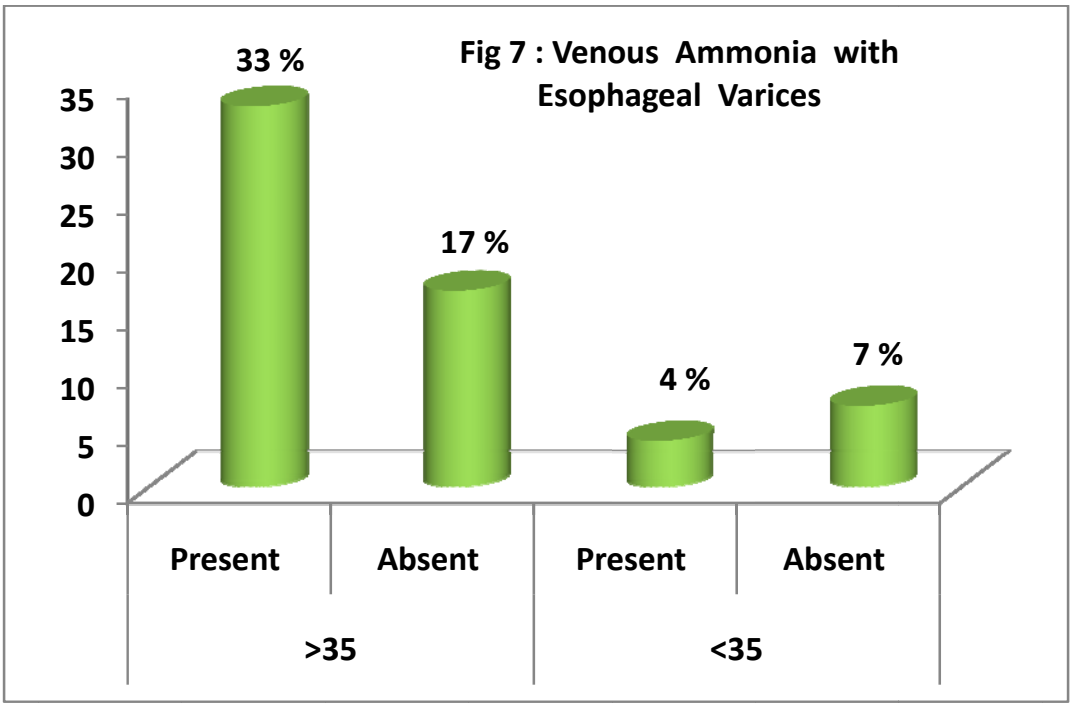
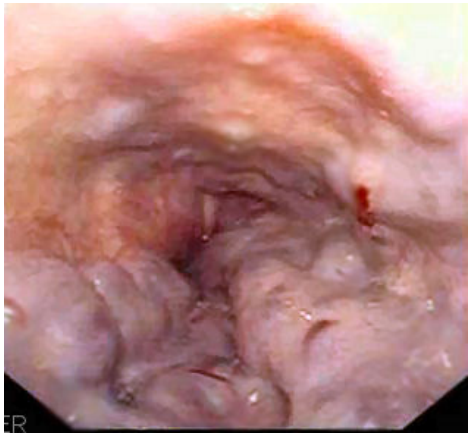


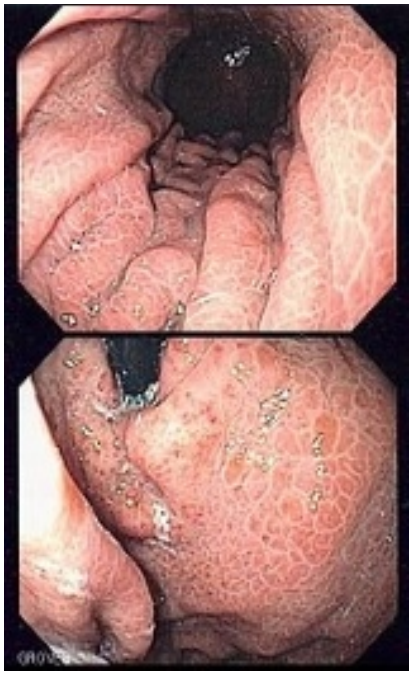
Fig 7 : Venous Ammonia with Esophageal Varices
33 %
17 %
4 %
7 %
35
30
25
20
15
10
5
0
Present
Absent
Present
Absent
>35
<35

LARGE ESOPHAGEAL VARICES



GASTRIC VARICES

PORTAL HYPERTENSIVE GASTROPATHY



PORTAL HYPERTENSIVE COLOPATHY

RECTAL VARICES

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PROFORMA

Name

Age

Sex

Occupation

Address

DDHD No

IP No

VOGD No

Occupation

Disease Duration

SYMPTOMS

Abdominal distension

Leg swelling

Jaundice

Altered sensorium

Blood vomiting

Malena

Weight loss

PAST HISTORY

Blood vomiting

Malena

Jaundice

Blood transfusions

Tattooing

Ear piercing

Jaundice

Diabetes

Hypertension

Other co morbidities – if any

PERSONAL HISTORY

Smoking	Amount	Duration
Alcohol	Amount	Duration

Marital status

Children

Siblings

I.V Drug abuse

Lactulose

Menstrual history

Examination :

Ht : cms	Wt: Kgs	BMI:
Pallor:	Icterus:	Cyanosis:
Clubbing:	Pedal edema:	LN:
Spider angioma:	Scartch marks:	
Palmar erythema:	Parotid enlargement:	KF ring
Gyneacomastia:	Asterxis:	RR :
JVP:	PR:	BP:

Abdomen examination :

ABD Distension:	Veins:	
Ascites	Liver span:	Spleen

Per rectal Ex :

CVS:

RS:

CNS : Grade of encephalopathy:

Investigation:

Hb:	TC:	DC
ESR :	Platelet count:	
BT:	CT:	P.Smear:
B.Ures:	B.Sugar	S.Cr.

Prothrombin time:

LFT:

T.Bil:	Direct:	Indirect:
SGPT:	SGOT	SAP:
T.Protein:	S.Albumin:	

Ascitic fluid :

Protein:	Albumin:	Cell count:
Cytology	SAAG : CTP score:	
Hbs AG:	HCV:	

S.Ceruloplasmin:

ANA:	Anti Sm Ab:	
Anti LKM Ab:	AMA:	Others

Venous Ammonia

<u>ULTRASOUND:</u>

Liver size	Texture : Nodule:
Spleen vein:	PV flow:
Splenic vein	SV flow:
Collaterals	Others:

UPPER GI SCOPY

ESOPHAGEAL VARICES:

Grade:	No.of columns:	Length:
Red signs:	Gastric varices:	PHG:

COLONOSCOPY:

Rectal Varices:	Colopathy:

Liver biopsy:

Others